

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Eric OLSON *et al.*

Serial No.: 09/061,417

Filed: April 16, 1998

For: METHODS AND COMPOSITIONS FOR
THERAPEUTIC INTERVENTION IN
CARDIAC HYPERTROPHY

Group Art Unit: 1642

Examiner D. Minh Tam

Atty. Dkt. No.: MYOG:029US/SLH

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

July 24, 2002
Date

Steven L. Highlander

DECLARATION OF RICK GORCZYNSKI UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Rick Gorczynski, do declare the following:

1. I am currently hold the position of Vice President, Research & Development at Myogen, Inc., licensee of the above-captioned application. My education and training includes an undergraduate degree in Biological Sciences from Cornell University and a Ph.D. in Cardiovascular Physiology from the University of Virginia, School of Medicine. I have worked since 1976 in the pharmaceutical industry, primarily in the cardiovascular drug discovery field. During my 25 years in the industry I have conducted and/or supervised

research directed at a variety of cardiovascular diseases including heart failure (acute and chronic), myocardial infarction, cardiac dysrhythmia, hypertension, renal disease, hyperlipidemias and thrombosis disorders. For the past 4 years I have been exclusively engaged in the discovery and validation of molecular drug targets for use in drug discovery in the field of heart failure. I am intimately familiar with the use of transgenic mice in the field of cardiac research and heart failure. A copy of my *curriculum vitae* is attached.

2. I am also familiar with the level of skill of scientists working in the field of cardiology and molecular biology as of the priority date of the referenced application. I consider one of ordinary skill in the art in this field of study to have a Ph.D. in biochemistry, chemistry, molecular biology, pathology or other related field, or an M.D., with 1-3 years of post-graduate study.
3. I have reviewed the specification and pending claims 1, 4, and 9 for the above-referenced case. The specification refers to the use of transfected cells and transgenic mice where NF-AT3 is either overexpressed (transfected cells) or continuously activated (transgenics) as a model for hypertrophy studies that are then held out as subsequently relevant for human studies. More specifically the specification refers to NF-AT3 transgenes lacking one or more phosphorylation sites present in wild-type NF-AT3, NF-AT3 transgenes lacking all the phosphorylation sites of the wild-type protein, and NF-AT3 transgenes lacking amino acids 1-137 of the wild-type NF-AT3 protein.
4. The inventors' paradigm, as defined through the transgenic models, was that activated calcineurin would directly bind to and dephosphorylate cytoplasmic NF-AT3. The

dephosphorylated NF-AT3 would then translocate into the nucleus where it would act as a transcription factor along with GATA-4, leading to induction of hypertrophic genes. It has not yet been shown, as the examiner correctly points out, that NF-AT3 is constitutively active or in a more active state in the hearts of hypertrophic patients. Nonetheless, NF-AT3 presents itself as an attractive candidate for therapy in cardiac hypertrophy. To that end, the inventors have targeted NF-AT3 both directly and indirectly to inhibit the onset of the transcription of hypertrophic genes.

5. I have reviewed the enclosed article by Ritter *et al.*, entitled "Calcineurin in Human Heart Hypertrophy," *Circulation*, 105:2265-2269 (2002) which supports the inventors' claims relating to NF-AT3 as a therapeutic target. The Ritter *et al.* authors set out to validate the observations made in transgenic mouse models by studying enzymatic activity and protein expression in cardiac tissue from human patients suffering from hypertrophic obstructive cardiomyopathy. While the article focuses more on the data regarding calcineurin levels in the hypertrophic hearts, the researchers also studied NF-AT2 phosphorylation levels in normal and hypertrophic heart tissue.

Ritter *et al.* showed that, in naturally hypertrophic tissues, NF-AT2 migrated at a higher rate on a 6% SDS gel, "compared with normal heart and identical to the NF-AT migration velocity of normal heart extracts treated with additional external calcineurin" (p. 2267), providing *in vivo* evidence from a human clinical setting of an altered NF-AT phosphorylation state in hypertrophied myocardium. This shows that NF-AT2, is in a more active, dephosphorylated form in the human hypertrophic heart, and also strongly implicates a similar finding for NF-AT3. Moreover, it validates the present inventors' notion of targeting NF-AT3 therapeutically to combat hypertrophy by interfering with the

NF-AT3 transcriptional cascade, whether by direct blocking (as in binding a molecule to NF-AT3) or by indirect effects (targeting the purported NF-AT3/GATA-4 complex).

6. With regard to the issue of using transfected cells to elucidate the interaction between NF-AT3 and GATA4, I have reviewed the attached scientific publications entitled "The Zinc Finger-containing Transcription Factors GATA-4, -5, and -6" (*J. Biol. Chem.* 275:50, 38949-38952, 2000), and "Remodeling muscles with calcineurin," (*BioEssays* 22:510-519, 2000). Based on the results set forth in these papers, it is clear to me that a person of ordinary skill (as defined above) would recognize that the art currently accepts that NF-AT3 does indeed interact with GATA-4, although this has not been shown directly. Perhaps the best information on this point comes from the latter paper, a mini-review of the state of the art, published over a year and a half ago. This article states that "GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT)" (p. 38951; also see Molkenin, *Cell* 93, 215; and Morin, *EMBO J.*, 19, 2046).

In conclusion, though no single experiment demonstrates a physical interaction between GATA-4 and NF-AT3, the aforementioned authors, as well as those of ordinary skill in the art in the field of cardiac biology, believe that such an interaction takes place. Further, it is my opinion that targeting this interaction using the approaches set forth in the present specification, with which I am quite familiar, is a valid approach to the treatment of hypertrophy. In particular, the use of GATA-4 mimetics and other small molecules that would interrupt the NF-AT3/GATA-4 interaction would be expected to interfere with NF-AT3's stimulation of the hypertrophic genes, providing a benefit to the patient.

7. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

July 3, 2002

Date

Richard Gorczynski

Rick Gorczynski, Ph.D.

CURRICULUM VITAE

RICHARD J. GORCZYNSKI, Ph.D.

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PROFESSIONAL EXPERIENCE

12/98-present

Vice President, Research and Development, Myogen Inc, Westminster, Colorado

Responsibilities

- Corporate Officer and member of the Myogen Executive Management Team
- Lead R&D activities focused on clinical development of one Phase II and one Phase III stage therapeutics for treatment of heart failure and related disorders; use of genomic, proteomic and biological techniques for identification of novel, disease-modifying compounds for reversal and prevention of heart failure; validation of molecular targets for drug discovery; identification of novel diagnostic markers for cardiac hypertrophy and heart failure
- Project Team Leader for Enoximone P.O. Development (until 1/00)
- Project Steering Committee member for BSF 208075
- Project Team Leader for Myosin Heavy Chain Project (collaboration between Myogen and a big pharma company)

Accomplishments

- In collaboration with Myogen scientific and medical advisory boards, established the company's Research Plan; established Target Validation techniques, HT Screening for the Company; built the R&D Group; managed external collaborations resulting in the identification of new technology for the Company.
- Project Plans for two Projects established: enoximone P.O. and Myosin Heavy Chain
- Planned and completed two successful meetings with the FDA Cardiorenal Division; resulted in agreement to proceed to Phase III with a heart failure therapeutic (enoximone); achieved alignment with the Agency on endpoints for four Phase II studies, product labelling language and scope of NDA.

6/98-11/98

Vice President, Research and Development and Boulder-Site Manager, Baxter, Hemoglobin Therapeutics Division, (Post-Baxter acquisition of Somatogen), Boulder, Colorado

Responsibilities

- Member of the Hemoglobin Therapeutics Division Management Team

- Lead Research and development activities at the Boulder-Site focused on the biological support of a Phase III-stage hemoglobin product candidate, DCLHb, research and development support for a Phase II-stage hemoglobin product candidate, rHb1.1 and research and development activities related to the discovery and advancement to clinical evaluation of a Second Generation hemoglobin product candidates
- Manage the Boulder-Site administratively, including facilities, safety, MIS and communications for R&D, Operations, Clinical, HR and Finance.

Accomplishments

- Defined new Boulder-Site organization in collaboration with the hemoglobin Therapeutics Division management team
- Identified several novel Second Generation hemoglobin product candidates

12/94 -6/98

Vice President, Research and Development, Somatogen, Inc., Boulder, CO

Responsibilities

- Corporate Officer and member of the Executive Management Group.
- Lead Research and Development activities at Somatogen; focused on 1) commercialization of lead product, Recombinant Human Hemoglobin (rHb 1.1) for oxygen-delivering and hematopoietic therapeutic indications 2) discovery and development of Second Generation recombinant hemoglobin products 3) development of non-hemoglobin technologies.
- Manage and coordinate Departments of Molecular Biology, Protein Engineering, Hemoglobin Research/Protein Chemistry, Pharmacology/Toxicology, Molecular Computation, Analytical Development, Purification Development, Formulation Development, and Fermentation Development (total of 65-70 people).

R&D Accomplishments

- In conjunction with the other Corporate Officers, positioned Somatogen for acquisition by Baxter Healthcare and prepared and presented the key technology summaries which lured Baxter to the table and eventually lead to an acquisition of Somatogen.
- Developed bioprocess for making clinical grade (GMP) rHb1.1 with successful scale-up demonstrating achievement of commercial expression and downstream yield targets; includes construction of host vector and strain, fermentation process, recovery and downstream purification system and associated analytical characterization; some of this was accomplished in collaboration with Eli Lilly and Co., our strategic corporate partner at that time.
- Advanced the understanding of hemoglobin biological effects including efficacy (oxygen delivery to tissue and potency), and safety related biologic effects; this work completed in support of commercial development of rHb1.1 and extended to the discovery of novel hemoglobin products.
- Initiated research on a promising new indication for rHb1.1: tumor radiation therapy sensitization.
- Initiated a drug-discovery project to identify new generation recombinant hemoglobin with enhanced therapeutic attributes; over 600 variant recombinant and

chemically modified/conjugated/cross-linked molecules constructed in three years; several lead molecules are undergoing advanced biological evaluation to ascertain suitability for human clinical testing. All have significantly improved properties.

- Three/four fold increases in rHb expression levels have been achieved (relative to commercial targets for rHb1.1).
- Completed several studies investigating the level of hematopoietic activity of rHb1.1 and other recombinant hemoglobins.
- Supervised preclinical discovery and development of a novel, in-licensed platelet substitute.

4/93 -12/94

Senior Director, Drug Discovery, Searle, Skokie, IL

Responsibilities

- Supervise the Cardiovascular Discovery Research Department (approximately 50 scientists; two sites: Skokie and St. Louis) with primary emphasis on atherosclerosis, thrombosis, arrhythmia, congestive heart failure and hyperlipidemia.
- Coordinate the process by which compounds from the Discovery Department are selected for, and transferred into, the Development Pipeline.
- Member R/D Executive Committee, Research Executive Committee and Development Executive Committee.
- Skokie Discovery Site Manager for facilities, safety and space administration.
- R/D liaison to the Corporate Licensing group.

Accomplishments

- Department Charter and Long Range Research Plan established.
- Five new Ph.D. hires in 1993 with backgrounds representing new directions in cardiovascular research (atherosclerosis/thrombosis/diabetes).
- Directed the design of a process by which Searle R/D will select Discovery stage compounds for formal Development; process consists of early toxicity, formulation, pharmacokinetic and chemical development studies of candidate molecules to optimize selection and the completion of critical analysis (development plan, marketing and financial) to support informal discussions on what to develop.
- Advanced new antiplatelet and antithrombotic agents into development (7/94); two antiplatelet compounds advanced to Phase III clinical development

8/89 - 4/93

Senior Director, Scientific and Product Affairs, Licensing/Business Development, Searle, Skokie, IL

Responsibilities

- Identification and follow-up of license and business development opportunities, with particular emphasis on Japan. Technical evaluation of all product license candidates.
- Manage process for full technical, medical and marketing review of candidates.
- Coordinate design of Development and Commercialization Plans for in-license candidates.
- Presentation of licensing opportunities to Searle top-management.

- Liaison between Licensing and Searle R/D.

Accomplishments:

- Two development collaborations initiated.
- One compound in-licensed (antidiabetic).

1/86 - 8/89

Director, Department of Cardiovascular Diseases Research, Searle, Skokie, IL

Responsibilities

- Supervise product discovery, chemical and biological research in the cardiovascular field with primary emphasis on hypertension, atherosclerosis, thrombosis and arrhythmia (staff: 45).

Accomplishments

- Four compounds into development (antihypertensive, and three antiplatelet agents).
- Two compounds in clinical study: antiarrhythmic and hypolipidemic.

9/85 - 1/86

Director, Biological Research Department, Searle, Skokie, IL

Responsibilities

- Supervised product discovery, biological research in four areas: cardiovascular, CNS, gastrointestinal and autotoxin mediated diseases (staff: 80).
- Department was reorganized 1/86 following restructuring of all R/D after Monsanto takeover of Searle.

8/83 - 9/85

Section Head Pharmacology, American Critical Care (Division of Baxter Travenol Corp) (formerly Arnar-Stone Laboratories), McGaw Park, IL

Responsibilities

- Supervised drug discovery, biological research in the cardiovascular, ophthalmic and CNS areas including beta-blockers, positive inotropic agents, antiarrhythmic agents, antiglaucoma agents and antiepileptic agents (staff: 13).

Accomplishments

- Five compounds into development (two beta-blockers, one antiglaucoma, one antiarrhythmic and one antiepileptic).
- Four IND's and one NDA (with approval).

9/80 - 8/83

Group Leader, American Critical Care (Division of American Hospital Supply Corp.) McGaw Park, IL,

Responsibilities

- Supervised drug discovery, biological research in the cardiovascular area (beta-blockers, cardiotonics and alpha blockers).

11/78 - 9/80

Senior Research Investigator, Arnar-Stone Laboratories (Division of American Hospital Supply Corp.), McGaw Park, IL,

Responsibilities

- Drug discovery in field of dopamine analogues and beta adrenergic receptor antagonists.

9/76 - 11/78

Research Investigator, Arnar-Stone Laboratories, McGaw Park, IL

Responsibilities

- Drug discovery in field of dopamine analogues and beta adrenergic receptor antagonists.

DRUG DEVELOPMENT EXPERIENCE

- Project Team Leader: enoximone P.O.; Phase II for treatment of ultra-advanced heart failure (myogen).
- Project Team Leader: Second Generation recombinant hemoglobin project (Somatogen).
- Designed the process used to select compounds for formal Development and Clinical Study (Searle).
- Liaison to Development Project Teams for all cardiovascular compounds accepted for development (Searle).
- Project Team Leader (American Critical Care).
- Coordinate design of Development and Commercialization Plans for in-license candidates.
- Development of an ultra-short acting beta-blocker - responsible for organizing and tracking development of a novel compound through all stages of preclinical development (raw material supplies, pharmacology, drug metabolism/pharmacokinetics, analytical assays, formulation, stability, etc.) and initial clinical trials.
- Member of three other project teams which are responsible for the development of a vasodilator, an antiarrhythmic agent and another ultra-short acting beta-blocker.

EDUCATION

1976 Ph.D., Physiology
University of Virginia
School of Medicine, Department of Physiology
Charlottesville, Virginia

Dissertation: The Microcirculatory Basis of Functional
Hyperemia in Striated Muscle (University Microfilms #76-25012)

Thesis

Advisor: Brian R. Duling, Ph.D., Professor of Physiology

1970 B.A., Biological Sciences
Cornell University
Ithaca, New York

TRAINING

- 1996 Somatogen: Performance Management System
- 1995 Somatogen: Project Management
- 1990 Searle: Introduction to Financial Analysis in Business (AMA)
- 1989 Searle: Introduction to Licensing (LES)
- 1989 Searle: Decision Making Skills: Consensus
- 1986 Searle: Interview Selection Skills
- 1986 Searle: Personnel Management System Training
- 1983 American Hospital Supply: Corporate Middle Management Course
- 1981 American Management Association: Project Management
- 1980 American Hospital Supply: Management Style and Effectiveness Training

AWARDS

American Critical Care President's Award for Scientific and Technical Excellence - 1979

Runner-up for American Critical Care President's Award for Scientific and Technical Excellence - 1978

PROFESSIONAL ACTIVITIES

Member, Editorial Board of the Journal of Cardiovascular Pharmacology - 1984 to 1994

Ad Hoc Reviewer for Microvascular Research, the American Journal of Physiology and the Journal of Pharmacology and Experimental Therapeutics, Blood

SOCIETIES

International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology (Scientific Steering Committee)

American Society for Pharmacology and Experimental Therapeutics

American Association for Advancement of Science

International Society for Heart Research

Licensing Executives Society

American Heart Association

PATENTS

Novel therapeutic and diagnostic agents for treatment of heart failure. Applied May, 1999.

Epoxy-Steroidal Aldosterone Antagonist and Angiotensin II Antagonist Combination Therapy for Treatment of Congestive Heart Failure. WO96/40257

SEMINARS

1. Department of Physiology, University of Virginia, Fall 1976. "The microcirculatory basis of functional hyperemia in striated muscle".
2. Department of Physiology, Medical College of Wisconsin, Fall 1977. "The microcirculatory basis of functional hyperemia in hamster striated muscle".
3. Cardiovascular Discussion Group, Skokie, IL, Fall 1982. "Mechanisms of inotropic selectivity".
4. Esmolol Symposium, Spring 1985. "Basic pharmacology of esmolol".

5. Kureha Chemical Industry, Tokyo, Fall 1989. "Platelet GPIIb/IIIa: a new target for discovery of novel antiplatelet agents".
6. University of Virginia, Graduate Study Colloquium, Winter, 1994. "Job Opportunities in the Pharmaceutical Industry."
7. IBC Conference Blood Substitute, 1996. "Measurement of the Efficacy of Hemoglobin-based Oxygen Carriers
8. International Symposium on Intensive Care and Emergency Medicine, Brussels, 1997. Preclinical update on rHb1.1
9. Tokyo Blood Substitutes Conference, 1997. "Comparison of Optro with Whole Blood using 31 P-NMR Spectroscopy"

PUBLICATIONS

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2. Spath, J.A., Gorczynski, R.J. and Lefer, A.M.: Pancreatic perfusion in the pathophysiology of hemorrhagic shock. Amer. J. Physiol., 226:443-451, 1974
3. Gorczynski, R. J., Spath, J.A. and Lefer, A.M.: Vascular responsiveness of the in situ perfused dog pancreas. Europ. J. Pharmacol., 27:68-77, 1974
4. Gorczynski, R.J. and Lefer, A.M.: Properties of the reticuloendothelial system of the cat. Proceed. Soc. Exper. Biol. & Med., 147:24-28, 1974
5. Gorczynski, R.J., Klitzman, B.M. and Duling, B.R.: Interrelations between contracting striated muscle and precapillary microvessels. Amer. J. Physiol., 235:H494-H504, 1978
6. Gorczynski, R.J. and Duling, B.R.: The role of oxygen in arteriolar functional vasodilation in hamster striated muscle. Amer. J. Physiol., 235:H505-H515, 1978
7. Borgman, R.J., Erhardt, P.W., Gorczynski, R.J. and Anderson, W.G.: Cyclopropylamine hydrochloride (ASL-7003): A rigid analogy of dopamine. J. Pharm. Pharmacol., 30:193-195, 1978

8. Gorczynski, R.J., Anderson, W.G., Erhardt, P.W. and Stout, D.M.: Analysis of the cardiac stimulant properties of (3,4-dihydroxyphenyl)-cyclopropylamine (ASL-7003) and 2-Amino-6,7-Dihydroxy-1,2,3,4-Tetrahydronaphthalene (A6,7DTN). J. Pharm. Exp. Therap., 210(2):252-258, 1979
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10. Erhardt, P.W., Gorczynski, R.J. and Anderson, W.G.: Conformational analogues of dopamine. Synthesis and pharmacological activity of (E)- and (Z)-2-(3,4-dihydroxyphenyl) cyclopropylamine hydrochlorides. J. Med. Chem., 22 (8):907-911, 1979
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13. Gorczynski, R.J., Anderson, W.G. and Stout, D.M.: N-aralkyl substitution of 2-amino-5,6-and -6,7-dihydroxy-1,2,3,4-tetrahydronaphthalenes. 1. Cardiac and pressor/depressor activities. J. Med. Chem., 24:835-839, 1981
14. Stout, D.M. and Gorczynski, R.J.: N-aralkyl substitution of 2-amino-5,6- and -6,7-dihydroxy-1,2,3,4-tetrahydronaphthalenes. 2. Derivatives of a hypotensive-positive inotropic agent. J. Med. Chem., 25:326-328, 1982
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28. Gorczynski, R.J., Murthy, V.S. and Hwang, T.F.: Beta-blocking and hemodynamic effects of ASL-8052. J. Cardiovas. Pharm., 6:1048-1059, 1984
29. Shaffer, J.E. and Gorczynski, R.J.: Role of alpha-adrenergic receptors in the intrinsic inotropic selectivity of dobutamine in anesthetized dogs. Canad. J. Physiol. Pharm., 63 (6):630-635, 1985

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